"New start" for energy metabolism - hope for people with rare diseases

The use of already approved drugs gives hope for new ways to treat rare diseases such as Leigh syndrome. This is demonstrated by the work of the CureMILS research consortium, which has led to the first successful treatments.

Without mitochondria, the human body lacks "fuel": inside the cells, mitochondria convert fats and carbohydrates from food into the body's own energy currency, ATP. If the cellular metabolism is disturbed, this can result in serious illnesses. One of these is maternally inherited Leigh syndrome, MILS for short, a rare disease in which a mutation of the MT-ATP6 gene on the mitochondrial DNA impairs the metabolism in the cell and thus the central nervous system (see box). Leigh syndrome, in which in the worst case entire areas of the brain die off, cannot currently be effectively treated or cured. The mechanisms underlying the disease have not yet been fully deciphered; one of the main obstacles is the lack of model systems that can be used to simulate the course of the disease in humans.

Reprogramming of cells reveals therapeutic approaches

With the reprogramming of somatic cells, scientists hope to come a big step closer to a therapy and even a cure for Leigh syndrome. To this end, researchers from the CureMILS network, which is funded by the German Federal Ministry of Education and Research (BMBF), are using skin cells from patients that are "transformed" into so-called induced pluripotent stem cells (iPSC) and can then be differentiated into various neuronal cells in the laboratory. "The human nerve cell models we have created are much better suited to researching Leigh syndrome than animal models that lack the corresponding DNA mutation," explains Professor Dr. Alessandro Prigione from Heinrich Heine University (HHU) in Düsseldorf, the head of the CureMILS consortium.

However, the researchers also want to overcome the lack of effective model systems by attempting to reprogram patient cells directly into neuronal cells. With such induced neural stem cells (iNSCs), the time-consuming process of obtaining iPSCs could be significantly shortened. "The reprogrammed neuronal cells can be further differentiated into 2D and 3D model systems," explains Dr. Ole Pless from the Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP) and responsible for a sub-project at CureMILS. "Thanks to refined differentiation technologies, nerve cell cultures and so-called brain organoids can be produced, which can be used to understand and evaluate the effect of drugs on areas of the brain that are particularly affected in MILS patients."

High-throughput screening provides high-quality "drug library"

Prigione and its partners have carried out a large-scale screening using reprogrammed nerve cells. Using a high-throughput process, they have tested more than 5,500 active substances for which extensive safety and efficacy data are already available and compiled them in a high-quality "substance library". The use of already approved drugs, known as repurposing or repositioning, could also quickly provide effective help for MILS patients and normalize mitochondrial metabolism, as gene therapy treatment approaches are still a long way off, according to Prigione.

One of the active substances tested at CureMILS is sildenafil, which is approved for the treatment of erectile dysfunction under the name Viagra®. The safety of the active ingredient is also already known and well researched in children. "In pediatrics, sildenafil is approved for the treatment of pulmonary hypertension in infants," says Prigione, "We were able to show that the active ingredient has a positive influence on intracellular calcium metabolism and the growth capacity of nerve cells in MILS patients."

Individual therapy successes confirm the researchers' approach

At the same time as these investigations in the research laboratory, Dr. Markus Schülke, Professor of Experimental Neuropaediatrics at the Charité in Berlin, was looking after a young MILS patient who had been in a coma for several weeks following a metabolic crisis with cardiac and muscle weakness and epileptic seizures and required intensive medical treatment. After weighing up all the risks and together with the parents, the treating doctors decided to try treatment with sildenafil.

The success proved the clinicians right: "The patient recovered quickly under the therapy and was able to breathe and move on his own again," reports Schülke. Further individual therapy trials in two children and two adults with a high mutation load for an MT-ATP6 mutation were carried out in Dusseldorf, Berlin, Munich and Bologna. According to Schülke, all patients tolerated sildenafil well and benefited from the treatment.

Based on the preclinical and clinical data, the European Medicines Agency (EMA) has now approved the use of sildenafil for MILS therapy in accordance with the Orphan Drug Designation (ODD) - a decisive step towards ensuring that other patients can also benefit from the treatment. The consortium is planning a Europe-wide multicenter study to clinically test the effect of sildenafil.

Translation: From the laboratory to patients

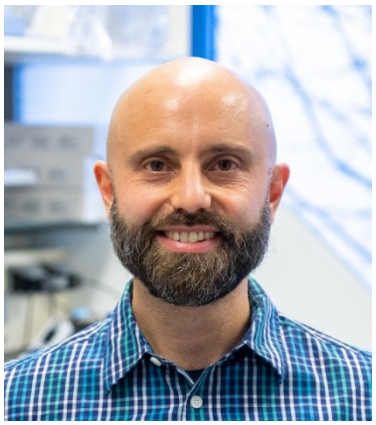
The work in the Cure-MILS network thus extends far beyond basic research. They have shown that there are already numerous drugs on the market that can help with rare diseases and enable the rapid translation of research results from the laboratory to the patients concerned. "We have provided a kind of 'research pipeline' for the repositioning of drugs and shown that the parallel investigation of extensive substance collections can lead to results much faster than was the case in the past," summarizes Alessandro Prigione. "In addition, the disease models we have developed not only point the way to effective treatment of MILS - this approach could also be applicable to other rare and previously incurable diseases."

Maternal Inherited Leigh Syndrome (MILS)

Maternal Inherited Leigh Syndrome (MILS) is a rare, genetic and progressive disease of the central nervous system caused by a disorder of mitochondrial metabolism. MILS occurs in around one in 100,000 newborns; those affected often suffer from symptoms such as muscle weakness, epilepsy, hearing and vision problems and a serious developmental disorder from birth. If the disease only manifests itself later, even supposedly trivial infections can lead to a metabolic crisis with hyperacidity of the blood and even coma. The life expectancy of those affected is usually only a few years.

CureMILS consortium

The CureMILS consortium brings together basic researchers and clinicians from Germany, Austria, Finland, the Netherlands, Luxembourg, Poland and Italy as well as patient organizations and partners from industry. The Federal Ministry of Education and Research (BMBF) supports the work of the research consortium led by Professor Alessandro Prigione through the European Joint Program on Rare Diseases (EJP RD). In the years 2021 to 2024, almost 830,000 euros will be provided for this purpose; from 2015 to 2019, the BMBF provided around 1.4 million euros to fund fundamental work for the network via the junior research group System-iPS led by Prigione.



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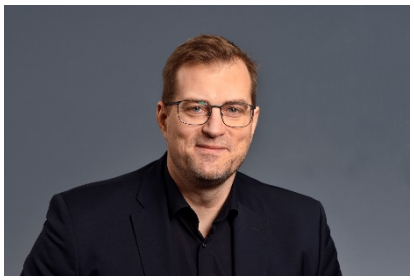

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